REMARKS

Reconsideration in view of the following remarks is respectfully requested. This invention relates to a method for chronically measuring the electrical activity of tissue samples in response to various chemical substances. The tissue sample is cultured on a multielectrode device which also measures the electrical cell potential of the sample while it is being cultured.

Claims 12, 14, and 16 are pending in this application, and have been rejected by the Examiner under 35 U.S.C. § 103(a). Applicants respectfully remind the Examiner that in order to properly establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all claim limitations. *See* MPEP 2143. As further elucidated below, the cited references, alone or in combination, do not meet the requirements of Section 103.

For the Examiner's convenience, pending claims 12, 14, and 16 are provided. No claim amendments are submitted in this response.

Pending Claims 12, 14, and 16

12. (Five Times Amended) A method of testing the chronic effect on neural or muscle tissue samples of chemical substances comprising:

providing a detector, wherein the detector comprises a plurality of microelectrodes on a substrate configured to contact the tissue sample and apply an electric stimulus to the tissue sample;

contacting said neural or muscle tissue sample with the plurality of electrodes;

measuring the electrical properties of the neural or muscle tissue sample;

adding said chemical substance to the neural or muscle tissue sample;

measuring the electrical properties of the neural or muscle tissue sample at a time which measures chronic response to said chemical substance; and

comparing said electrical properties before and after said addition of said chemical substance to determine whether said added chemical substance has had an influence on the neural or muscle tissue sample.

14. The method of claim 12 for testing the effect on neural or muscle tissue samples of chemical substances as medicines, wherein the step of adding chemical substance to the neural or muscle tissue sample comprises adding said chemical substance in a selected concentration to the neural or muscle tissue sample.

16. The method of claim 12 for testing the effect on neural or muscle tissue samples of chemical substances as medicines, wherein the chronic measuring step takes place at least three days after said addition step.

Claim Rejections Under 35 U.S.C. § 103(a)

Gahwiler et al. in view of Gross et al.

Claims 12, 14, and 16 stand rejected under 35 U.S.C. §103(a) as being upatentable over Gahwiler et al. (Neuroscience, 1982, 7; 1243-1256), in view of Gross et al. (J. of Neuroscience Methods 5: 13-22, 1982). Specifically, the Office Action states:

> "Gahwiler et al. 1982, teach a method of testing the effect of chemical substances (acetylcholine) on neuronal tissue (hippocampal sections) and measuring the electrical properties (see experimental procedures on page 1243 and 1244) before and after addition of said substance (see results and figures). Although the prior art used standard electrophysiological techniques for recording the electrical properties, the prior art specifically does not teach providing a detector comprising plurality of microelectrodes on a substrate for contacting the tissue sample (i.e., the device or apparatus)."
>
> "Gross et al teach an apparatus (see material and methods/figures) for observing a physical and chemical property of a tissue or cells comprising providing photoetched electrodes integrated into the floor of a tissue culture chamber

(i.e. providing a substrate with planar electrodes disposed on the same plane as the substrate) and a cell culturing means. (page 13). Gross et al teach recording the electrophysiological potentials with electrodes integrated into the tissue culture plate would allow the long term monitoring of neuronal activity. It would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to us e the apparatus designed by Gross in a method of Gahwiler et al to measure the electoral properties before and after addition of chemical substances because Gross et al suggests that the apparatus disclosed in obviously designed for long term cultures. The motivation to use this apparatus to achieve the obviously designed for long term cultures. The motivation to use this apparatus to achieve the obvious benefits is clearly suggested by Gross (see page 21, last paragraph). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the apparatus as taught by Gross et al for measuring and comparing waveforms or electrical properties of neural tissue before and after the addition of chemical substances as taught Gahwiler et al because the apparatus is designed to measure the effect of different concentrations of the chemical substance on tissue and comparing the electrical properties of long term cultures."

Applicants disagree that the combination of Gahwiler et al. ("Gahwiler") in view of Gross et al. ("Gross") would have rendered the claims obvious under Section 103.

Gahwiler et al. teaches measurement of cell potentials from rat hippocampus that has been cultured using the roller-tube technique. As the name implies, the roller-tube method utilizes an apparatus that rotates while maintaining tissues. Thus, the tissue must be transferred from this apparatus to a standard measurement apparatus when electrophysiological measurements are desired. After obtaining the measurements, the tissue is put back into the roller tube. Chronic measurements cannot be obtained, because in order to maintain the tissue, it must be cultured in the rotating roller-tube. Serial measurements, if taken, involves transferring the tissue sample between the roller-tube and the measurement apparatus, and each time placing electrodes in (a different area of) the sample.

Gross et al. mentions a device that cultures mouse spinal tissue cells on a multielectrode plate. The multielectrode plate measures electrical properties of the cells which are dissociated neurons. The cited reference does not suggest that the device can

measure electrical properties of neural or muscle tissue samples. Furthermore, there is no suggestion that the device can be used in a roller-tube method.

Therefore, Applicants point out that one of skill would not be from those references above, motivated to use the device of Gross with the method of Gahwiler since Gahwiler does not suggest the need for a device that both cultures the sample and records electrical activity from the sample. Furthermore, even if used, the device of Gross would not be able to maintain a tissue sample or record the electrophysiological activity of neural or muscle tissue, because it was designed to only culture clumps of cells and record electrical activity in the general fluid presence of the clump.

Even if the cited references were combined, it is highly unlikely that the device of Gross would be able culture and/or record electrical activity of the sample while rotating (e.g., due to the input/output connections for the electrodes).

Also, a combination of Gahwiler and Gross would still not result in the claimed method. The step of measuring a chronic response of neural or muscle tissue would not be taught, as required by the claims under consideration.

Prima facie obviousness has not been established, and withdrawal of the rejection is respectfully requested.

Gahwiler in view of Giaever et al.

Claims 12, 14, and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gahwiler et al. (Neuroscience, 1982, 7; 1243-1256) in view of Giaever et al. (U.S. Patent 5,187,096). Specifically, the Office Action states:

> "Giaever et al teach an apparatus (see claims) for observing a physical and chemical property of a tissue or cells comprising plurality of electrodes integrated into the floor of a tissue culture chamber (i.e. providing a substrate with planar electrodes disposed on the same plane as the substrate) and cell culturing (column 2, Summary of the invention) means. Giaever et al teach by using this apparatus, the activities of cultured cells that are attached to the surfaces could be followed continuously in real time. The recording of extracellular electrophysiological potentials with electrodes integrated into the tissue culture plate would allow the long term monitoring of cell activity to change in the physical environment and drugs (column 3 and 4). It would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to use the apparatus

> designed by Giaever et al in a method of Gahwiler et al to measurer the electrical properties before and after the addition of chemical substances because Giaever et al suggests that this apparatus is obviously designed for long term cultures. The motivation to use this apparatus to achieve the obvious benefits is clearly suggested y Giaever et al. (see column 3, lines 23-55). therefore it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the apparatus as taught by Giaever et al for measuring and comparing waveforms or electrical properties of neural tissue before and after the addition of chemical substances as taught by Gahwiler et al because the apparatus designed by Giaever is fore measuring the effect of different concentration of the chemical substances on tissue and comparing the electrical properties of long term cultures."

Applicants disagree and respectfully request that the Examiner reconsider the teachings of Giaever et al. ("Giaever"). Gahwiler has been discussed above. Giaever describes an apparatus that can only "detect and measure the following: cell attachment, cell spreading, lateral motion of cells, porosity, areas involved in adhesion plaques, cell-substrate spacing, and vertical cell motion" (3:26-30). The method is accomplished by measuring changes in the impedance of the electrodes (2:57-64). Accordingly, Giaever does not teach a device that measures an electrical property of a tissue sample. Also of note is that Giaever's sample is not a tissue. Generally, it is a population of about 20-50 cells (2:41-42).

Therefore, one of skill would not be motivated to use a device that does not measure electrical cell potentials of tissue samples in a method that requires measurement of electrical potentials from tissue samples. Also, if combined, it is clear that a reasonable expectation of success does not exist because Giaever's device is not designed for culturing of tissue samples or measurement of electrical activity from the sample. Furthermore, the teachings of the cited references in combination do not meet all the limitations of independent claim 12.

Gahwiler in view of Giaever does not render obvious the rejected claims. Withdrawal of the rejection is therefore respectfully requested.

SUMMARY

Applicants have responded to each matter of substance raised in this final Office Action and believe the application to be in condition for allowance. Should the Examiner have any questions, comments, or suggestions, she is urged and invited to contact the Applicants' representative at the number listed below. Should an interview be considered desirable, please feel free to also contact Applicants' representative for a personal or telephone interview.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned representative so that prosecution may be expedited.

In the unlikely event that the Patent Office determines that an extension and/or other relief is required as a result of this statement, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to our **Deposit account no. 03-1952** referenced Docket No. **356972020100**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: February 28, 2003 By: _____

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